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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/295,464	04/19/99	ONG	C 80135-0

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EXAMINER	
SCHNIZER,R	
ART UNIT	**PAPER NUMBER**
1632	6

DATE MAILED: 05/08/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary	Application No. 09/295,464	Applicant(s) Ong
	Examiner Richard Schnizer	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-14 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-14 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☒ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: CA 2205888

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

A preliminary amendment was received and entered as Paper No. 4 on 4/19/99. Claims 1-14 are under consideration in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

With respect to claims 7 and 8, the specification, while being enabling for making a mouse with the recited DNA sequences integrated into its genome, does not reasonably provide enablement for making any other organism with the recited DNA sequences integrated into its genome. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The invention is a method of producing a eukaryotic organism comprising two heterologous DNA sequences integrated into the genome of the organism. The invention allows

the identification of genes having patterns of expression restricted to specific cell types. Thus the scope of the claims is limited to multicellular organisms. The specification contemplates the production of transgenic mice comprising the nucleic acids of the invention, and teaches methods of selecting for integration events (see pages 28-30). Currently, the production of transgenic animals in this manner depends on the use of embryonic stem (ES) cells, and this technology is well developed in the mouse system. The state of the art with respect to the use of ES cells from other organisms is set forth by Mullins (1996) who teaches that techniques for the use of non-mouse ES cells are based on those developed for mouse ES cells, and that these techniques are in need of further refinement (pages 37 and 38). Specifically, chimeric non-mouse animals have been created by the injection into blastocysts of freshly isolated ES cells, and totipotency of these cells has been demonstrated. However, attempts to culture non-mouse ES cells result in differentiation and loss of totipotency. Culturing of ES cells is essential for the selection process required in the instant invention. Therefore the state of the art for the production of non-mouse animals encompassed by the claims is highly unpredictable. The specification offers no guidance in this respect. It is also noted that the scope of the claims encompasses plants, fungi, and certain algae which comprise differentiated cells. The specification offers no guidance or examples as to how to practice the invention in these systems. Thus, in view of the breadth of the claims, the lack of predictability of the art, and the lack of guidance in the specification, a skilled artisan would be required to perform undue experimentation without reasonable expectation of success in order to produce non-mouse versions of the claimed organisms.

With respect to claims 9-14, the specification, while being enabling for identifying promoters or genes through the use of a promoterless integration DNA construct, does not reasonably provide enablement for identifying promoters or genes using DNA constructs which comprise promoters. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The invention comprises DNA constructs useful for identification of promoters having restricted expression. The constructs must be used together. One construct comprises a promoter operably linked to a first indicator component. The other construct **comprises** a splice acceptor and a second indicator construct. This second construct could also comprise a promoter operably linked to the sequence encoding the second indicator component. The specification does not disclose any use for the constructs of the invention other than for the identification of genes and promoters.

Neither the specification nor the prior art teach how a skilled artisan could use two integrating constructs, both comprising promoters operably linked to indicator components, to identify promoters or genes. The prior art teaches many promoter trap vectors which are promoterless, and claims 1-8 of the instant invention are also drawn to a promoterless construct.

In view of the state of the prior art and the lack of teaching or examples in the specification, a skilled artisan would have to perform undue experimentation order to use the entire scope of the claimed constructs for the purpose taught by the specification.

This rejection can be overcome by amending claims 9-14 to recite a DNA construct wherein the second indicator component is not operably linked to a promoter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5 are indefinite because the method steps are not concordant with the purpose set forth in the preamble. Specifically, the claims are methods of detecting are target gene, but the steps do not recite the detection of any target gene. As written, the claim describes a promoter trap, but fails to list steps wherein the promoter, or its gene, is detected. It is suggested that the claims be amended one of two ways. First, Applicant may wish to amend these claims to recite methods of detecting promoters, rather than genes, and to include a final step reciting detection of a promoter. In this respect it is noted that claim 6 is drawn to isolating sequences flanking the insertion site, and could be easily amended to recite a method of detecting (or isolating and identifying) genes. Alternatively, claims 1-5 could simply be amended to recite steps associated with detecting genes, *i.e.* isolating flanking sequences and determining open reading frames.

Claims 7 and 8 are indefinite because the method steps are not concordant with the purpose set forth in the preamble. The invention is a method of making a eukaryotic organism by transfecting a cell and subsequently growing that cell into an entire organism. In addition to steps (I) and (ii), the claim should recite steps describing how the transfected cell is grown into an organism. In view of the enablement rejection above, it is suggested that the claim be limited to a method of making a transgenic mouse. The method should then recite steps in which transfected ES cells are selected, inserted into blastocysts, the blastocysts are transplanted into pseudopregnant mice, developed to term, and the resulting chimeric offspring are characterized for integration of the heterologous DNAs. Optionally, further steps for breeding chimeric mice, identification of fully transgenic offspring, and subsequent crosses to produce homozygotes could be included.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al (Proc. Nat. Acad. Sci. USA 88: 11368-11372, 12/1991), in view of Andres et al (J. Biol. Chem. 268(2): 1383-1390, 1993).

When a reference used in a rejection under 35 U.S.C. 102 describes all the limitations of a claim with the exception of a characteristic which is inherent to the composition, it is proper to include an extra reference teaching that the omitted characteristic is, in fact, inherent. See MPEP 2131.01 paragraph III.

Chen teaches plasmid λRTHB which comprises an intron immediately upstream of a cDNA encoding the rat farnesyltransferase α subunit. Introns must, by definition, comprise a splice acceptor site. Chen also teaches that farnesyltransferase is a heterodimer of α and β subunits, both of which are required for activity. See abstract; page 11368, column 1, last sentence of second paragraph; and page 11369, column 2, lines 8-11 of first full paragraph. Chen is silent as to any inherent activity attributable to the α subunit. Andres teaches that the farnesyltransferase α subunit plays a direct role in catalysis. See abstract. Because this characteristic is inherent in the α subunit, Chen teaches all the limitations of the claim.

Thus the claim is anticipated by Chen.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moosmann et al (Nucl. Acids Res. 24(6): 1171-1172, 3/1996), Severne et al (EMBO J. 7(8): 2503-2508, 1988), Baskar et al (J. Virology 70(5): 3207-3214, 5/1996), Choi et al (Mol. Cell. Biol. 11(6): 3070-3074, 6/1991), and Jang et al (Enzyme 44(1-4): 292-309, 1990).

Moosmann teaches separate DNA expression constructs encoding β galactosidase α and ω fragments under the control of the CMV promoter, and their simultaneous use in mammalian cells. Moosmann suggests that the sequences encoding the α and ω fragments should be used in gene expression studies in cultured cells and in animals, particularly in "dual expression monitoring systems in which the α and ω peptides are brought under distinct genetic control." See entire document. Moosmann does not teach a DNA construct comprising a splice acceptor or an IRES.

Severne teaches that the vector of Moosman comprises the CMV promoter. See page 2504, column 1, lines 20 and 21 of Fig.1 legend.

Baskar teaches that the CMV promoter displays restricted expression in the mouse. See entire document, especially abstract.

Choi teaches that incorporation of a generic intron between a promoter and a gene of interest causes 5- to 300-fold increases in transgene expression in mice. See entire document, especially abstract.

Jang teaches that internal ribosomal entry sites are useful tools in the construction of high yield expression vectors. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the constructs of Moosman by incorporation of an intron upstream of the α and/or ω fragment open reading frames, and by the inclusion of an IRES element. One would have been motivated to do so in order to increase the expression of the corresponding peptides. One of ordinary skill in the art appreciates that the signal intensity in an enzyme-driven reporter system will increase with the concentration of the enzyme if the substrate is in excess. It is desirable to increase signal intensity because this allows greater sensitivity.

Thus the invention as a whole was *prima facie* obvious.

This rejection may be overcome by including the limitation that the sequence encoding the second indicator component is not operably linked to an expression control sequence.

Conclusion

No claim is allowed.

Claims 1-8 and 14 appear to be free of the art.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday-Friday from 7:30 to 4:00 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at 703-308-2035. The FAX phone number for art unit 1632 is 703-308-0294.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Richard Schnizer, Ph. D.

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800